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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/402,680	01/10/00	SCHWARZ	H BHV-313.01

EXAMINER

HM12/0208

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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/402,680	Applicant(s) Schwarz et al.
	Examiner Michele Flood	Group Art Unit 1651

☒ Responsive to communication(s) filed on *Nov 27, 2000* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *43-75* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *43-75* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on November 27, 2000. Acknowledgment is made of Applicant's cancellation of Claims 9-42; and, the claims are withdrawn from further consideration by the Examiner, as being drawn to a non-elected invention

Acknowledgment is made of newly submitted Claims 43-75.

The rejection made under 35 U.S.C. 102 paragraph, has been overcome by Applicant's amendment of the claims.

The rejection made under 35 U.S.C. 103 has been overcome by Applicant's amendment of the claims.

Claims 43-75 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65-66, 71 and 72 are rejected under 35 U.S.C. 112, second paragraph as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 66 contains a misspelling in line 1. Applicant can overcome the rejection by replacing "cryopercipitated" with cryoprecipitated.

An extra period, which should be removed, appears at the end of the sentence of Claim 71.

Claim 72 recites the limitation "the method according to claim 72" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

3. Claims 43-48, 50-55, 57-60, 62-64, and 73-75 are rejected under 35 U.S.C. 102(e) as being anticipated by Evans et al. (C or O).

Applicant claims a method for inactivating microorganisms, wherein the microorganisms are viruses, and pyrogens present in biological materials comprising: incubating the biological material in the presence of an alkyl phosphate-free detergent solution containing at least one eluotrophic salt in a total concentration of at least 200mM; and eluting the biological material from the detergent solution, and preparations prepared thereof.

Evans (US Patent 5,989,421) teaches a method for the extraction of DNA from a suspension of cells, comprising the steps of 1) supplying a suspension of cells to a filter apparatus, 2) if necessary, filtering off medium in which the cells are suspended, 3) applying a lysis solution to the cells and incubating the cells for a period sufficient to release DNA therefrom; and 4) filtering off lysis solution containing DNA. Other embodiments of the method taught by Evans include; 5) applying the filtrate from step (4) to an ion-exchange medium; 6) washing the ion-exchange medium with a first solution to elute material other than DNA; and 7) washing the ion-exchange medium with a solution to elute the DNA. In Column 2, lines 20-24, Evans teaches that the method can be directed to a culture of animal cells or body fluids, such as blood. In Column 4, lines 32-62, Evans teaches incubation of cells in the presence of a lysis solution for a period of 3 to 15 minutes, wherein the lysis solution 4 M guanidine thiocyanate, 0.1 m sodium acetate, 5% Triton X-100™, and 3 M urea. Other chaotrophic agents, which can be used in the method taught by Evans include guanidine hydrochloride, sodium iodide, sodium perchlorate and salts of guanidine such as guanidine thiocyanate. Evans teaches other non-ionic detergents, such as Tween™, can be used in his method. See Column 4, lines 32-47. In Column 5, lines 3-8, Evans teaches that the procedure for the lysis of the cells can be repeated several times to increase the yield of DNA. Purification of the biological material is carried out by ion exchange media such as DEAE, see Column 5, lines 9-18. In Column 10, lines 61-67 bridging Column 11, lines 1-58, Evans teaches a method for the extraction and purification of genomic DNA from blood comprising the steps of reacting a blood solution with a solid carrier such that the blood was

adsorbed onto the solid carrier, and incubating the adsorbed blood solution with a lysis solution comprising 4 M guanidine thiocyanate, 5% Triton X-100™, 0.1 M sodium acetate and urea at concentrations from 0.5 to 4 M, followed by the elution of DNA from the nuclei of the cells. Evans does not expressly teach a method for inactivating microorganisms and pyrogens present in biological materials, however, the process steps, the ingredients used, the materials to be treated, and the experimental parameters and conditions taught by Evans are the same or essentially the same as disclosed in the claimed invention. Thus, the result would be the same or essentially the same result as disclosed in the instant application. Moreover, the lytic solution taught in the method of Evans lyses the cells of microorganisms, and comprises denaturing solvents and detergents which are well known in the art to inactivate microorganisms, pyrogens, and viruses. The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. (C or O) in view of Commission of the European Communities, "Ad Hoc Working Party on Biotechnology/Pharmacy Guidelines" (BH).

Applicant claims a method for inactivating microorganisms, wherein the microorganisms are viruses, and pyrogens present in biological materials comprising: incubating the biological material in the presence of an alkyl phosphate-free detergent solution containing at least one eluotrophic salt in a total concentration of at least 200mM; and eluting the biological material from the detergent solution. Applicant further claims a method, wherein incubating is performed between 1 hour and 5 hours.

The teachings of Evans are set forth above. Evans does not teach a method wherein the step of incubation is performed in the prescribed periods of time of between 1 hour and 5 hours. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the incubation times taught in the method of Evans to provide a method for inactivating microorganisms and pyrogens, and wherein the microorganisms are viruses because Evans expressly teaches that the incubation procedure for the lysis of the cells can be repeated several times. Because Evans teaches his lytic solution as a solution which lyses cells, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to increase the incubation time of the lytic process taught by Evans because it is well known in the art that the lysis of cells contained in a biological material kills or inactivates the cells. Moreover, Evans teaches that the repeat of the lytic process further purifies a biological material.

It also would have been obvious to one of ordinary skill in the art to modify the incubation times taught in the method of Evans to provide a method for inactivating microorganisms and

pyrogens, and wherein the microorganisms are viruses because the Commission of the European Communities (CEC) teaches the criteria necessary for designing methods for testing for the efficacy of a viral inactivation procedure or purification methods for the production of biological materials wherein the safety and control of the product from viral contamination is required. In one approach, the CEC teaches the deliberate addition of virus loads to a crude material to be purified and to different fractions obtained during the purification stages, and its removal or inactivation during the subsequent stage of purification and/or inactivation is determined. One of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the incubation holding times taught in the method of Evans because at the time the invention was made it was well in the known art that a measure for the inactivation of viruses or the reduction factor by the addition of a test virus could be calculated from the decadic logarithm of the quotient of initial and final virus titers, as taught by the European Guideline EC III/8115/89-EN of the Commission of the European Communities. Furthermore, the total reduction factor was old and well known in the art at the time the invention was made as a calculation of the sum of the reduction factors of individual, subsequent inactivation measures.

In absence of showing criticality or unexpected results, it would have been in the purview of one skilled in the art to select different holding or incubation times to obtain different results in the end product, such as characteristic physicochemical or biological active properties of the end

product. Process limitations are given little or no weight in determining the patentability of the final product in the absence of criticality or unexpected results in the final product.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 46, 61 and 65-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michalski et al. (B) in view of Evans et al. (C or O), and further in view of admitted prior art.

Applicant claims a method for inactivating microorganisms, wherein the microorganisms are viruses, and pyrogens present in biological materials comprising: incubating the biological material in the presence of an alkyl phosphate-free detergent solution containing at least one eluotrophic sodium chloride salt in a total concentration of at least 200mM; and eluting the biological material from the detergent solution. Applicant further claims a method, wherein the biological material is a blood factor is selected from the group consisting of factor VII, factor XII, factor XI and prekallikrein. Applicant further claims a method for inactivating microorganisms and pyrogens present in an activated prothrombin complex comprising: reacting a mixture containing the activated prothrombin complex with a solid carrier such that the activated prothrombin complex is adsorbed on the solid carrier; washing the solid carrier having the activated prothrombin complex adsorbed thereon; incubating the solid carrier having the activated prothrombin complex adsorbed thereon in the presence of a tri-n-butyl phosphate (TNBP)-free TWEEN®-80 solution, the detergent containing 30 mg/mL of sodium chloride; eluting the

purified biological material from the tri-n-butyl phosphate (TNBP)-free TWEEN®-80 solution. Applicant further claims a method wherein the mixture is cryoprecipitated fresh human plasma. Applicant further claims a method wherein the solid carrier is DEAE-Sephadex® A-50. Applicant further claims a method wherein the incubating step is conducted at 26°C for 1 hour; and, further comprising diluting the mixture and solid carrier with water following the incubation for 1 hour at 26°C for an additional 1 hour to facilitate readsorbtion of the activated prothrombin complex onto the DEAE-Sephadex®, and washing the DEAE-Sephadex® having the activated prothrombin complex adsorbed thereon.

Michalski teaches a process for the viral inactivation and purification of the PPSB fraction of human plasma in the preparation of a human thrombin concentrate. The method taught by Michalski includes the following steps (1) adsorption of cryoprecipitated plasma on a DEAE-SEPHADEX® which is prewashed in citrate buffer containing 0.2M to 0.23M sodium chloride and a step of elution up to 0.5 sodium chloride; (2) activation of the thrombin by incubation with calcium chloride, followed by (3) solvent/detergent viral inactivation in 0.3% TnBp/1% Tween-80®; (4) purification of the thrombin by means of ion exchange chromatography; and, thrombin preparation by ultrafiltration. See Column 2, lines 45-68 and Column 3, lines 1-56. Michalski teaches the claimed invention except that Michalski does not teach a method for inactivating microorganisms and pyrogens present in an activated prothrombin complex comprising the instantly claimed steps of incubating the solid carrier having the activated prothrombin complex adsorbed thereon in the absence of tri-n-butyl phosphate and eluting the purified biological

material from a tri-n-butyl phosphate-free TWEEN®-80 solution. However, it would have been obvious to one of ordinary skill in the art to modify the teachings of Michalski by replacing the step of inactivation taught by Michalski because Evans teaches a method for lysing a suspension of cells in the presence of a lysis solution for a period of 3 to 15 minutes, wherein the lysis solution 4 M guanidine thiocyanate, 0.1 m sodium acetate, 5% Triton X-100™, and 3 M urea. One of ordinary skill in the art at the time the invention was made would have been motivated and one would have had a reasonable expectation of success to substitute the method of viral inactivation by taught by Michalski for the method of viral inactivation taught by Evans because Evans teaches his lytic solution as a solution which is effective in the lysis of cells contained in a body fluid such as blood, and it is well known in the art that the lysis of cells render the cells inactive or kills the cells.

With regard to the claim limitation of a incubating and eluting the biological material in the presence of a tri-n-butyl phosphate-free TWEEN®-80 solution, it also would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the lytic solution taught by Evans because Michalski teaches that TWEEN®-80 solution in combination with a detergent is effective in the inactivation of viruses in blood products. Thus, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success that the substitution of the TRITON™ taught in the lytic solution taught by Evans for the TWEEN®-80 taught by Michalski would have the functional effect of viral inactivation when combined with a detergent. One of ordinary skill in the art would have been further motived to

substitute one for the other because Evans expressly teaches that the employ of either TRITON™ and TWEEN® in the making his lytic solution is interchangeable.

With regard to the claimed limitation that the solid carrier is DEAE-Sephadex® A-50, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the claimed solid carrier because Applicant readily admits that the type or model of the solid carrier used in the instantly claimed method is not critical to achieve the functional effect of the result. For instance, on page 9, line 27 bridging page 10, lines 1-18, Applicant lists numerous solid carriers which can be used in the performance of the claimed invention. One of ordinary skill in the art at the time the invention was made would have motivated and one would have had a reasonable expectation of success to use DEAE-Sephadex® A-50 or any other functional equivalent solid carrier in the performance of the claimed method because Michalski clearly teaches the use of the adsorption of cryoprecipitated plasma on a DEAE-SEPHADEX® solid carrier model.

As the references indicate the various proportions and amounts of the ingredients, incubation holding times, number of washings of the solid carrier and readsorbtion thereon of the reacted ingredients used in the claimed method, they would be routinely optimized by one of ordinary skill in the art practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Michalski et al. (B) in view of Evans et al. (C or O), and further in view of Isakkson et al. (A or N), and further in view of Eibl et al. (D).

Applicant further claims a method for inactivating microorganisms and pyrogens present in an activated prothrombin complex comprising: reacting a mixture containing the activated prothrombin complex with a solid carrier such that the activated prothrombin complex is adsorbed on the solid carrier; washing the solid carrier having the activated prothrombin complex adsorbed thereon; incubating the solid carrier having the activated prothrombin complex adsorbed thereon in the presence of a tri-n-butyl phosphate (TNBP)-free TWEEN®-80 solution, the detergent containing 30 mg/mL of sodium chloride; eluting the purified biological material from the tri-n-butyl phosphate (TNBP)-free TWEEN®-80 solution. Applicant further claims a method wherein the eluting is performed using a heparin solution such that a purified suspension of activated prothrombin complex is obtained.

The combined teachings of Michalski and Evans are set forth above. Neither Michalski nor Evans teach a method wherein the eluting is performed using a heparin solution such that a purified suspension of activated prothrombin complex is obtained. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combined teachings of Michalski and Evans by adding heparin to the eluting solution because Isakkson teaches a process for the inactivation of virus in blood products by adding heparin to an elution solution in the production of a prothrombin complex product. For instance, Isakkson

teaches a process for the inactivation of virus in blood products, such as a plasma protein, in a one step process using a suitable combination of temperature and concentration of salt of at least 0.5 M with a salting out effect according to the Hofmeister series. The virus inactivation step includes the addition of detergents, TWEEN® and/or TRITON®. Prior to the step of viral inactivation, Isakkson teaches a method of diluting antithrombin from blood using a Heparin Sepharose gel. One of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the combined teachings of Michalski and Evans by adding the step of elution using heparin taught in the method of Isakkson because at the time the invention was made it was well known in the art to add heparin to the end product when producing the prothrombin complex, in order to prevent an activation of prothrombin, as evidenced by the teachings of Eibl in Column 1, lines 7-41. Thus, the claimed invention is no more than the additive effect of well known ingredients and method steps in the making of well known products.

As the references indicate the various proportions and amounts of the ingredients, incubation holding times, number of washings of the solid carrier and readsorbtion thereon of the reacted ingredients used in the claimed method, they would be routinely optimized by one of ordinary skill in the art practicing the invention disclosed by each of the references.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Michael Wityshyn whose telephone number is (703) 308-4743.

mcf

January 31, 2001

LEON B. LANKFORD, JR.
PRIMARY EXAMINER